

Remarks

After entry of the amendment, claims 93-143 are pending.

Claims 1-92 have been canceled without prejudice.

Claims 93-143 are supported by the originally filed claims and throughout the specification.

No issues of new matter should arise and entry of the amendment is respectfully requested.

Rejection under 35 U.S.C. § 103

Claims 40, 41 and 44-89 are rejected under 35 U.S.C. § 103(a) as being obvious over Liu *et al*, *Proc. Natl. Acad. Sci. USA* 93:8618-8623 (1996) in view of Mendelsohn, *Clinical Cancer Res.* 3:2703-2707 (1997) and Hortobágyi, *Oncology* 11:11-15 (1997).

Applicant respectfully traverses the rejection and respectfully submits that the presently claimed invention is unobvious over the combination of cited references.

The Federal Circuit in *In re Mayne*, 41 USPQ2d 1451, 1455 (Fed. Cir. 1997) held:

"With a factual foundation for its *prima facie* case of obviousness shown, the burden shifts to applicants to demonstrate that their claimed [compositions] possess an unexpected property over the prior art. *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995). An applicant may make this showing with evidence that the claimed property or advantage exhibits some superior property or advantage that a person of ordinary skill in the relevant art would find surprising or unexpected. *Id.*

The basic principle behind this rule is straight forward — that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.

Id. An examination for unexpected results is a factual, evidentiary inquiry...."

Applicant respectfully submits that the data in the specification clearly shows that the presently claimed compositions, kits and methods provide superior results that would be unexpected in view of the teachings in the cited references. Applicant respectfully submits that the unexpectedly superior results shown in the specification rebut the obviousness rejection set forth by the Patent Office.

The issue in *In re Mayne* was whether the applicants data regarding low immunogenicity provided unexpectedly superior results to obtain a patent for their claimed fusion proteins. In other words, a showing of unexpectedly superior results for a particular method would have been sufficient to obtain patent protection for composition claims.

Applicant respectfully submits that composition claims are clearly patentable if the applicants provide a showing of unexpectedly superior results in a method of using the composition. This is supported by the Federal Circuit's holding in *In re Mayne, supra*, and by the MPEP. For example, MPEP § 716.02(a) states:

SUPERIORITY OF A PROPERTY SHARED WITH THE PRIOR ART IS EVIDENCE OF NONOBVIOUSNESS

Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties ... can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) (Evidence showing that the claimed herbicidal compound was more effective than the closest prior art compound in controlling quackgrass and yellow nutsedge weeds in corn and soybean crops was sufficient to overcome the rejection under 35 U.S.C. 103, even though the specification indicated the claimed compound was an average performer on crops other than corn and soybean.). See also *Ex parte A*, 17 USPQ2d 1716 (Bd. Pt. App. & Inter. 1990) (unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut *prima facie* obviousness even though there was no evidence that the compound was effective against all bacteria.)

The MPEP teaches that evidence of unexpectedly superior results is sufficient to obtain patent protection for claims directed to a compound or composition. In other words, a showing of unexpectedly superior results does not merely confer patentability to the methods of use — it also confers patentability to the compositions.

MPEP § 716.02(a) is consistent with the Federal Circuit's holding in *In re Chupp*, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) where the Federal Circuit held that "[e]vidence that a compound is unexpectedly superior in one of a spectrum of common properties, as here, can be enough to rebut a *prima facie* case of obviousness."

Applicants respectfully submit that MPEP § 716.02(a) and the Federal Circuit's holdings in, for example, *In re Mayne* and *In re Chupp* support the patentability of the pending claims.

In the present application, it has unexpectedly been discovered that claimed compositions of immunoconjugates and chemotherapeutic agents delay tumor growth longer than one would expect for an additive anti-tumor effect of the individual components.

For example, in Example 3 of the application, it has unexpectedly been discovered that a tumor growth delay of twelve days was observed when SCID mice with tumors derived from NCI N417 cells were treated with huN901-DM1 in combination with cisplatin and etoposide, whereas a tumor growth delay of four days was obtained in animals treated with either huN901-DM1 or cisplatin and etoposide. The tumor growth delay of 12 days represents a synergistic effect, as it is 50% longer than the eight days one would expect for an additive anti-tumor effect of the individual treatments.

As a further example, as seen in Example 4 of the application, in a similar experiment involving treatment with docetaxel alone, huN901-DM1 alone or a combination of docetaxel and huN901-DM1, treatment with docetaxel or huN901-DM1 alone resulted in tumor growth delays of 8 days and 20 days, respectively. In contrast, treatment with the combination of docetaxel and huN901-DM1 resulted in complete tumor regression in all the treated animals. The tumor was eradicated in 3 out of 6 animals in this treatment group, resulting in cures lasting greater than 200 days. In the remaining 3 animals in this group, there was a tumor growth delay of 52 days, which is 24 days longer than the calculated additive effect of the treatment with docetaxel and huN901-DM1 alone.

Other such unexpected, synergistic and otherwise surprising results are found in Examples 2, 5, 6 and 7 of the pending application.

Applicants respectfully submit that the unexpected results shown in the Examples in the application are commensurate in scope with the pending claims. In support thereof, with respect to the maytansinoid used in the immunoconjugates in the Examples, Applicant submits herewith a Declaration under 37 C.F.R. § 1.132 by Walter A. Blättler, Ph.D. (hereafter "the Blättler Declaration). The Blättler Declaration states that the results shown in the Examples would have been the same or substantially the same if the maytansinoid compound used in the Examples was substituted with a different maytansinoid compound.

The superior, unexpected, synergistic and otherwise surprising results utilizing the claimed kits and compositions are not taught or suggested in Liu *et al.*, Mendelsohn, or Hortobágyi, either alone or combined.

The references cited by the Patent Office do not suggest that the claimed combination of immunoconjugates and chemotherapeutic agents would provide unexpectedly superior results.

Liu is directed to the administration of immunoconjugates by themselves. There is nothing in Liu that would suggest that an immunoconjugate in combination with a chemotherapeutic agent would provide unexpectedly superior results in the treatment of cancer.

Mendelsohn is directed to the combination of antibodies and chemotherapeutic agents. Mendelsohn does not disclose or suggest the use of the claimed immunoconjugates.

Hortobágyi is directed to the combination of chemotherapeutic agents with other chemotherapeutic agents. Hortobágyi does not disclose or suggest the use of the claimed immunoconjugates.

The results described in Mendelsohn do not teach or suggest that combining a monoclonal antibody, let alone the claimed immunoconjugate, and a chemotherapeutic agent results in expected, synergistic effects. For example, in the section entitled "Hypothesis 5" discussed on page 2705, experiments involving combined therapy with anti-EGF receptor monoclonal antibody with doxorubicin; mAB225 or 528 in combination with cisplatin; and mAB 225 in combination with paclitaxel are described. After describing the results, it is mentioned in the last paragraph of column 1 that "[t]he mechanism of these *additive* effects are under investigation in our laboratory." (Emphasis Presented).

Hortobágyi states, on page 12, lines 24-30, citing reference 7 (i.e., Bissery, M.C. et al., *Proc. Am. Assoc. Cancer Res.* 35:327, 1994), that "[s]ynergies, or at least additive effects, were observed in studies with two- and even three-drug combinations, including docetaxel, cyclophosphamide (Cytoxan, Neosar), fluorouracil (5-FU), vinorelbine, methotrexate, and etoposide (VePesid)." The abstract mentions that docetaxel was evaluated in combination with doxorubicin, 5-fluorouracil, cyclophosphamide, mitomycin C, vincristine, vinblastine and vinorelbine (methotrexate and etoposide were not used as asserted in Hortobágyi). The only results discussed are the maximum tolerated dose of each drug that could be administered in

combination without additional toxicity. There is no teaching or suggestion in the abstract that combinations of the specific anticancer agents tested led to synergistic effects.

More importantly, there is no evidence in the cited references that one skilled in the art would expect immunoconjugates to produce unexpectedly superior results when used in combination with chemotherapeutic agents, and there is no evidence that chemotherapeutic agents and/or monoclonal antibodies are interchangeable with or equivalent to immunoconjugates.

Applicant respectfully submits that the presently claimed composition, kit and method claims are clearly patentable, and that their patentability is supported by the MPEP § 716.02, the Federal Circuit's holding in *In re Mayne*, *supra*, and the Federal Circuit's holding in *In re Soni*, 34 USPQ2d 1684 (Fed. Cir. 1995). The claim at issue in *In re Soni* was directed to a composition. To quote from *In re Soni*:

On appeal, Soni concedes that the prior art relied upon establishes a *prima facie* case of obviousness. Thus, the sole question for resolution is whether Soni carried its burden of rebutting the *prima facie* case of obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) (*prima facie* case of obviousness shifts burden to applicant to come forward with rebuttal evidence or argument).

The reference cited describe relevant compositions containing polyethylene and a conductive filler. We need not focus on the specific disclosures of the references since it is conceded that the correctness of the rejection boils down to the question whether the data in Soni's patent specification show that the compositions of the claims exhibit unexpectedly improved physical and electrical properties compared to lower molecular weight compositions.

...One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results," *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward — that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.

Mere improvement in properties does not always suffice to show unexpected results. In our view, however, when an applicant demonstrates *substantially* improved results, as Soni did here, and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary. Soni, who owed the PTO a duty of candor, made such a showing here. The PTO has not provided any persuasive basis to question Soni's comparative data and assertion that the demonstrated results were unexpected.

Applicant respectfully submits that the facts in the instant case are analogous to the facts in *In re Soni*. Applicant has shown that the claimed composition of an immunoconjugate and chemotherapeutic agent provides unexpectedly superior results in treating cancer. Accordingly, the composition, kit and method claims are patentable. Moreover, the Patent Office has not provided any evidence that the results shown in the specification are expected.

In view of the above, Applicants respectfully submit that the presently claimed invention is unobvious over the combination of cited references, and respectfully request that the rejection under 35 U.S.C. § §103 be withdrawn.

Conclusion

Applicant respectfully requests an early and favorable reconsideration and allowance of pending claims 93-143. The Examiner is encouraged to telephone the undersigned to expedite prosecution of this application.

Respectfully submitted,

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